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MEDICAL STAFF CONFERENCE

Hyperuricemia—Pathogenesis and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The topic for Medical Grand Rounds this morning is hyperuricemia, with particular emphasis on pathogenesis and treatment. The patient will be presented by Dr. Glaser.

DR. GLASER:† The patient was a 57-year-old white man who died in this hospital two years ago of chronic renal failure and Gram-negative bacteremia. He gave a strong family history of gouty arthritis, with two uncles and a grandfather having had gouty arthritis. At 15 years of age the patient noted the onset of arthritis, which went undiagnosed and untreated for many years. When he was 49 years old, his arthritis was treated for the first time with dexamethasone (Decadron®), aspirin, and codeine by his private physician.

He was first seen at this hospital in 1962 at age 52 for the chief complaint of confusion and was diagnosed as having adrenal insufficiency. At that time the diagnosis of gouty arthritis was also made on the basis of extensive tophi involving the subcutaneous tissues and virtually every peripheral joint. A draining tophus was observed on the left ear, as well as typical uric acid crystals in joint fluid. His serum uric acid was 11.2 mg per 100 ml, and he was treated with probenecid and colchicine. Between 1962 and 1969 he had multiple hospital admissions for fever and hepatosplenomegaly, and several lymph node biopsies were done. In 1966 he was treated with allopurinol in doses of 300 to 400 mg per day. On the 400 mg dose his serum uric acid decreased to 6.6 mg per 100 ml, and some softening of the tophi was observed. Even so, during this period he developed progressive renal failure and hypertension in association with Gram-negative bacteremia which led to his death.

DR. SMITH: We are fortunate to have Dr. Hibbard Williams with us today to discuss the background, pathogenesis and treatment of hyperuricemic states.

DR. WILLIAMS:* Our subject today is "the gout." The rather devastating nature of this particular ailment was perhaps best described by Thomas Sydenham in 1683.

> "The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by severe pain in the great toe; more rarely in the heel, ankle, or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follow chills and shivers, and a little fever. The pain, which was at first moderate, becomes more intense. With its intensity the chills and shivers increase. After a time this comes to its height, accommodating itself to the bones and ligaments of the tarsus and

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metatarsus. Now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected that it cannot bear the weight of the bedclothes nor the jar of a person walking in the room. The night is passed in torture, sleeplessness, turning of the part affected and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint, and being worse as the fit comes on. Hence the vain effort, by change of posture, both in the body and the limb affected, to obtain an abatement of the pain." [1]

Even today this is an extremely accurate description of the clinical syndrome of gout. The culprit in this malady is uric acid, the oxidized end product of purine metabolism in man.[2] Uric acid is rather poorly soluble in water to the extent of only 6.5 mg per 100 ml. It has a pKa of 5.75, the ionized species being more soluble and thus accounting for the favorable response to alkali therapy in patients excreting large amounts of uric acid. In body fluids the urate ion forms the sodium salt which is estimated to reach saturation at 6.4 mg per 100 ml of serum, a concentration very close to that of the normal serum uric acid level. It is known, however, that this compound may exist in the super-saturated state in a fairly stable form, and uric acid levels as high as 100 mg per 100 ml serum have been observed in certain myeloproliferative disorders. The miscible pool of uric acid in normal subjects is about 1200 mg, with a turnover of about 700 to 800 mg per day, of which approximately one-third is excreted by intestinal uricolysis and the remaining two-thirds by renal excretion, with approximately 300 to 500 mg of uric acid appearing in the urine per 24 hours. A specific urate binding globulin has been described, but this may represent a laboratory phenomenon since the binding seems to occur primarily at 4° C with much less binding at 37° C.

Renal Excretion of Uric Acid

The mechanisms for the renal handling of uric acid deserve comment before we go on to pathogenetic mechanisms (Chart 1). Uric acid is freely filtered by the glomerulus and between 98 percent and 100 percent is reabsorbed in the proximal renal tubule. An amount equal to 10 to 15 percent of that filtered is secreted more distally in the proximal tubule, accounting for

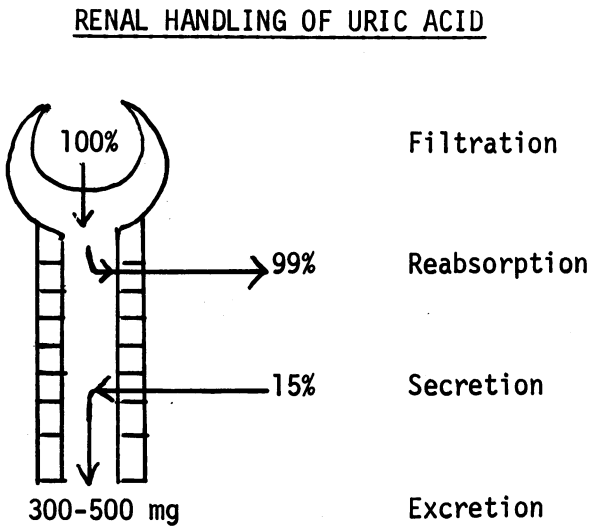

Chart 1.—Mechanisms for the renal handling of uric acid.

the daily excretion of about 300 to 500 mg of uric acid per 24 hours. A number of compounds, both drugs and organic acids, affect the renal handling of uric acid and have been of particular interest recently. Sodium and glucose both tend to inhibit the tubular reabsorption of uric acid in the proximal tubule and are thereby mildly uricosuric. The amino acid, glycine, appears to stimulate secretion of uric acid and is also uricosuric.

The cholecystographic dyes have recently been shown to be uricosuric in man, a factor which may be important in the renal toxicity of these compounds.[3] A number of other drugs affect the renal handling of urate, and one of the more common ones is aspirin, which has a dual effect in this regard. In low dosage aspirin favors uric acid retention, while doses above 4 gm per day are uricosuric. In low doses inhibition of secretion alone leads to urate retention, but in high doses inhibition of both secretion and reabsorption leads to uricosuria as the effect to decrease reabsorption predominates. In fact, probably all of the uricosuric agents, such as probenecid and sulfinpyrazone, have this dual effect on the tubular handling of urate, although in doses recommended for treatment of hyperuricemia they are, of course, uricosuric.

In addition to these drugs there is a group of organic acids, particularly lactate, beta-hydroxybutyrate and acetoacetate, which inhibit urate secretion and lead to hyperuricemia. Therefore,

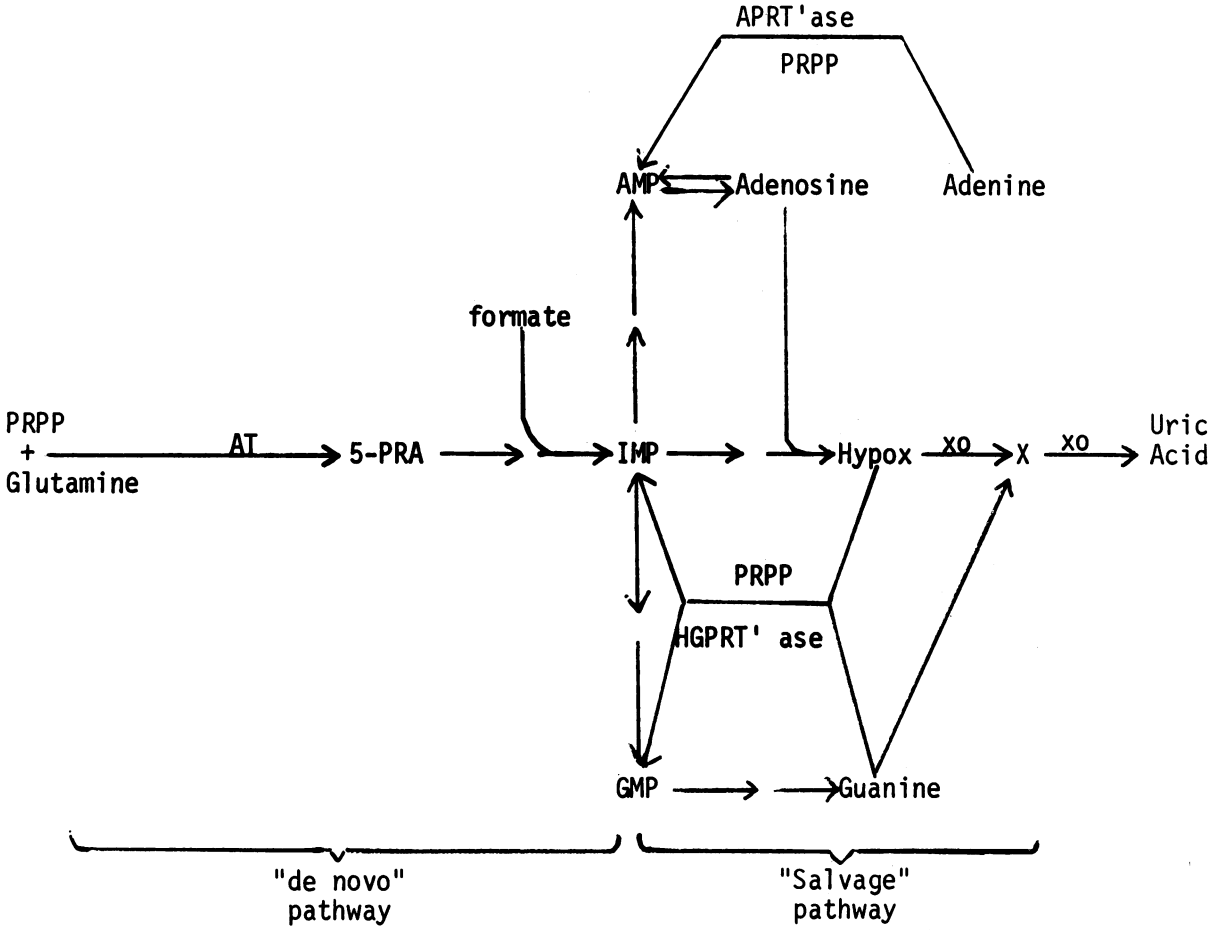

Chart 2.—Metabolic pathways in nucleotide and purine synthesis. For abbreviations see text. Additional abbreviations are: AT—amidotransferase; Hypox—hypoxanthine; X—xanthine; XO—xanthine oxidase.

any state associated with chronic lactic acidosis or the accumulation of acetoacetate and beta-hydroxybutyrate will lead to hyperuricemia, such as diabetic ketoacidosis or glycogen storage disease.

Metabolic Source of Uric Acid

The metabolism of the purine nucleotides (adenosine monophosphate and guanosine monophosphate, both essential for the normal synthesis of nucleic acids and other metabolic processes in the cell), is shown in Chart 2. As a result of the synthesis of these two purine mononucleotides, uric acid is produced as an end product, being synthesized directly from xanthine and hypoxanthine under the influence of the enzyme xanthine oxidase.[4] Two major metabolic pathways control the synthesis of these two nucleotides, the *de novo* pathway and the salvage pathway. The *de novo* pathway begins with a reaction which utilizes phosphoribosylpyrophosphate (PRPP) and glutamine to form 5-phosphoribosylamine (5-PRA). A number of subsequent metabolic steps then lead to the synthesis of the first purine nucleotide molecule, inosine monophosphate (IMP), which can in turn be converted to adenosine monophosphate (AMP) and guanosine monophosphate (GMP). The first reaction in the *de novo* pathway is rate limiting and is exquisitely sensitive to feedback inhibition by the products, GMP and AMP. In addition to this pathway and perhaps of greater quantitative significance is the salvage pathway, which converts the purines adenine, hypoxanthine and guanine to AMP, IMP and GMP respectively. Adenine phosphoribosyl transferase (APRT'ase) and hypoxanthine-guanine phosphoribosyl transferase (HGPRT'ase) are the two enzymes which control these interconversions of purines and nucleotides. Both of these enzyme systems utilize PRPP. The *de novo* path-

TABLE 1.—*Pathogenetic Mechanisms in Hyperuricemia and Gout*

Renal—30 percent	*Overproduction—70 percent*
Drugs	Idiopathic
Hypertension	Hemolytic disease
Obesity	Myeloproliferative disease
Chronic renal disease	Psoriasis (Sarcoidosis)
Lead and beryllium	Lesch-Nyhan
Alcoholism	Glycogen storage disease
Ketoacidosis	
Glycogen storage disease	
Nephrogenic diabetes insipidus	
Parathyroid disease	

way is similarly subject to feedback inhibition such that the accumulation of end products GMP, IMP and AMP will decrease their own synthesis.

Pathogenesis of Hyperuricemia

The pathogenesis of the hyperuricemic states in man is outlined in Table 1. In the clinical syndrome of gout approximately 30 to 40 percent of patients develop hyperuricemia because of some decrease in the renal excretion of uric acid and approximately 60 to 70 of patients because of overproduction of uric acid. Differentiation between these two basic mechanisms is helpful in evaluating the pathogenesis and treatment of hyperuricemia. Consideration of the syndromes associated with decreased renal excretion of uric acid involves a wide variety of conditions. A number of drugs are associated with hyperuricemia, the more important ones being aspirin, pyrazinamide and the thiazide diuretics.[5] The thiazide diuretics have an interesting action in man. In clinical practice these diuretics frequently cause hyperuricemia, probably by inhibition of tubular secretion. However, if all of the sodium and fluid lost with the administration of these diuretics is replaced, the drug actually becomes uricosuric. The drug has a dual effect on the renal excretory mechanism for uric acid related to the total body sodium and water content. Unfortunately, the exact molecular mechanisms involved in these actions are not known. Clinically the drugs when used in the treatment of heart failure or other fluid detention states are usually associated with hyperuricemia.

Hypertension and obesity are frequently associated with hyperuricemia. This probably involves a decreased renal excretion of uric acid. Chronic renal failure of any cause may be associated with hyperuricemia, apparently because of decreased filtration of urate. Lead and beryllium toxicity are associated with hyperuricemia apparently by inhibition of the renal secretion of uric acid. Alcoholism, diabetic ketoacidosis and glycogen storage disease, type I, are all associated with hyperuricemia on the basis of decreased renal excretion of urate as organic acids accumulate in the body. In the case of alcoholism and glycogen storage disease, the organic acid is lactate; in ketoacidosis they are beta-hydroxybutyrate and acetoacetate. Recently nephrogenic diabetes insipidus has been associated with hyperuricemia although the mechanism for this is not well understood. It appears not to be related to circulating levels of vasopressin. Both hypoparathyroid and hyperparathyroid states have been associated with hyperuricemia; again, the mechanisms have not been identified.

The overproduction mechanism accounts for a larger percentage of patients with gout, but a smaller number of specific syndromes have been identified with this mechanism.[4] Both hemolytic disease and the myeloproliferative disorders are associated with hyperuricemia on the basis of increased nucleoprotein turnover delivering to the metabolic pool large amounts of purines which must be disposed of as uric acid. This is particularly important in the treatment of myeloproliferative diseases with chemotherapy.

Psoriasis also is associated with hyperuricemia, a finding related to the extent of the involvement of the skin. This probably is due to the increased turnover of the nucleoproteins seen with extensive psoriatic disease. An interesting clinical triad of sarcoidosis, psoriasis and gout has also been described. The Lesch-Nyhan syndrome is a very important, rare, sex-linked disorder associated with pronounced hyperuricemia and overproduction of uric acid in association with severe mental retardation, choreoathetosis and self-mutilation. This syndrome has been the focus for much of the research in hyperuricemia and gout during the last five years. For completeness, in addition to the renal mechanism, overproduction of uric acid has also been demonstrated in glycogen storage disease. Once these causes of hyperuricemia are eliminated we are left with a large group of patients who have idiopathic overproduction of uric acid. There are several

TABLE 2.—*Possible Mechanisms for the Overproduction of Uric Acid in Gout*

1. HGPRT'ase deficiency
Complete
Partial
2. APRT'ase deficiency
3. Abnormal PRPP amido transferase
4. Abnormal glutamine metabolism
5. Increased PRPP formation
6. Abnormal glutathione reductase

possible pathogenic mechanisms which have been studied in the last few years in an attempt to explain the overproduction in these patients (Table 2).

In the past five years the enzyme HGPRT'ase has assumed an important role in our understanding of the pathogenesis of gout (Chart 2). It was noted in 1967 that the erythrocytes and skin fibroblasts of patients with the Lesch-Nyhan syndrome lack the enzyme HGPRT'ase, thus leading to a defect in the salvage pathway of hypoxanthine and guanine conversion to IMP and GMP, respectively.[6] Despite the fact that this disease and this enzyme defect have received a great deal of study since that period of time, we are still not absolutely certain as to the reason this enzyme defect leads to pronounced overproduction of uric acid. There are several theories which have been proposed, none of which is entirely satisfactory. A defect in this enzyme step might lead to deficient production of IMP and GMP, both of which feed back on the *de novo* pathway. Release of feedback inhibition would lead to increased *de novo* synthesis of IMP, AMP and GMP by the *de novo* pathway with subsequent overproduction of uric acid in an attempt to maintain normal intercellular levels of these nucleotides. Second, accumulation of PRPP, presumably because of failure to utilize it in the salvage pathway, may force the *de novo* pathway into greater synthesis. Third, hypoxanthine and xanthine which do accumulate in this syndrome may stimulate the amidotransferase enzyme and thereby increase *de novo* synthesis. Although the basic mechanism for increased urate synthesis is not determined as yet, the severity of the clinical syndrome and the severity of the hyperuricemia in the Lesch-Nyhan disease indicate the importance of this salvage pathway in normal nucleotide metabolism and the control of uric acid synthesis. Recently it has been demonstrated that erythrocytes from a small group of patients with gout have a partial defect in HGPRT'ase activity. These patients are adults with overproduction hyperuricemia, gouty arthritis and a group of unusual neurological symptoms in some of the patients. Enzyme activity is approximately 5 to 10 percent of normal, and this apparently leads to the overproduction of uric acid and perhaps bears some relationship to the neurological abnormalities.

The APRT'ase enzyme, which converts adenine to AMP has been shown to be deficient in several members of a large family, none of whom had hyperuricemia or gout. However, at least one patient with a deficiency of APRT'ase has now been shown to have significant hyperuricemia and gout. In a small number of patients an abnormal PRPP amidotransferase has recently been demonstrated. The abnormality in this enzyme appears to be an inability to respond to the normal feedback inhibition by AMP and GMP, thus leading to increased production of urate by the *de novo* pathway. An increase in PRPP formation forcing synthesis by the *de novo* pathway has been described in two conditions: the hyperuricemia associated with HGPRT'ase deficiency and with glycogen storage disease. Finally, an abnormal glutathione reductase has been described in a group of patients with hyperuricemia and gout. The exact relationship of this abnormal enzyme to the hyperuricemia is not known. Despite the elegant studies which have gone into the elucidation of pathogenetic mechanisms of gout, the molecular basis for the hyperuricemia remains an enigma in most patients with this interesting disorder.

Therapeutic Considerations

Before turning to a specific consideration of modes of therapy for hyperuricemia, some comments on why and when to treat patients seems pertinent (Table 3). There are two major reasons for treating hyperuricemia: first, prevention of chronic arthritis, which can be both painful and debilitating, and, second, the prevention of chronic renal damage.[7] The incidence of gouty arthritis seems to be related directly to both the length of time hyperuricemia is present and the absolute serum level of uric acid. The higher the serum level and the longer it is present, the more likely the patient is to develop

TABLE 3.—*Outline of the Treatment of Hyperuricemia*

- A. When and Why?
  - Prevention of arthritis
  - Prevention of renal damage
- B. Methods
  1. Diet
  2. Alkali
  3. Uricosurics
     - Probenecid
     - Sulfinpyrazone
     - Benziodarone
     - (Cholecystographic dyes)
  4. Allopurinol
     - Efficacy
     - Complications
     - Interactions
  5. Colchicine

acute gouty arthritis. Therefore, one of the advantages of treatment is prevention of the gouty arthritis and the subsequent damage to the joints produced by this particular form of arthritis. The second reason for treating patients, prevention of chronic renal damage, is less well documented. Patients with severe chronic tophaceous gout who succumb to the disease have an incidence of severe renal damage of approximately 20 to 25 percent. What is not known is the relationship of this renal damage to the serum level or the length of time hyperuricemia is present. That is, does the patient with modest hyperuricemia of 8 to 9 mg per 100 ml damage his kidneys over a period of time without symptoms and before gouty arthritis develops? I believe the answer to this is yes, but the data is not complete enough to determine this with any certainty. Long-term prospective studies, such as those in progress at the San Francisco Kaiser Hospital by Dr. Geoffrey Fessel, are needed to determine the effect of asymptomatic hyperuricemia on renal function. However, because of this potential danger, as well as the attempt to prevent gouty arthritis, most workers in the field suggest that patients with uric acid levels persistently above a level of 9 mg per 100 ml be treated for hyperuricemia regardless of whether they have gouty arthritis or evidence of renal damage.

Forms of Therapy

What forms of therapy are available? Diet is the least effective form of therapy for hyperuricemia. If one places a patient with hyperuricemia on a purine-free diet, one can reduce the uric acid level approximately 0.5 to 1.0 mg per 100 ml at best. Therefore, in severe hyperuricemic states this would not be sufficient to bring the uric acid level into normal range. Excess purines in the diet should be avoided, but a purine-free diet is rarely of significant help to the patient with hyperuricemia and gout.

Systemic alkali therapy is useful in two circumstances: in the patient receiving uricosuric agents who already has pronounced overexcretion of uric acid and in the patient with a myeloproliferative disease who receives chemotherapy. Alkali should be used in this circumstance because of the tremendous load of uric acid presented to the renal tubules as increased nucleoprotein catabolism occurs.

The uricosuric agents, probenecid and sulfinpyrazone, are effective and safe methods of treatment of hyperuricemia.[8] Probenecid has been used for nearly 20 years and has an extremely high degree of safety. Its major toxicity is gastrointestinal irritation and bleeding; there have been very few other serious side effects of therapy. For this reason, it is recommended by many physicians as the primary drug in the treatment of hyperuricemia. It may not be effective in patients with chronic renal failure, and in some patients with very large excretion of uric acid it may not add much to the already overworked renal excretory mechanisms. In addition, it poses a potential danger to the patient by increasing the uric acid concentration in the urine and thereby increasing the potential for uric acid neuropathy, although there has been little actual documentation of this potential danger.

Benziodarone is a new uricosuric agent which seems to affect primarily the renal secretion of uric acid rather than affecting primarily reabsorption as do the other uricosuric drugs. Cholecystographic dyes appear to be uricosuric, and this effect may account for the occasional renal toxicity seen after gall bladder examinations. Allopurinol, a more recently developed drug used in the treatment of hyperuricemia, is very effective in lowering serum uric acid levels by inhibiting the enzyme xanthine oxidase which catalyses the oxidation of hypoxanthine and xanthine to uric acid. Significant toxicity has been reported with the drug, namely cholestatic jaundice, skin eruptions, vasculitis and xanthine ne-

phropathy. The latter interesting complication, presenting as acute obstructive uropathy secondary to xanthine precipitation, has occurred in two circumstances: in patients with the Lesch-Nyhan syndrome treated with allopurinol and in patients with severe myeloproliferative disorders receiving both chemotherapy and allopurinol.[9] In these latter patients allopurinol must be administered judiciously and alkali therapy must be initiated because of the accumulation of xanthine in the renal collecting system and the potential for obstructive uropathy. Finally, colchicine remains the treatment of choice for the acute attack of gout.

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